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L15: Entry 5 of 5 File: DWPI Oct 11, 1989

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TITLE: Pharmaceutical compsns. with controlled release - comprise microporous support contg. active substance in incorporated form and distributed in crystalline form of nanometre ranges

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PRIORITY-DATA: 1988IT-0020145 (April 8, 1988)

PATENT-FAMILY:

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EP 336014 A	October 11, 1989	E	008	
DE 3872382 G	July 30, 1992		000	A61K009/18
EP 336014 B1	June 24, 1992	E	010	A61K009/18
ES 2042700 T3	December 16, 1993		000	A61K009/18
IT 1216570 B	March 8, 1990		000	
US 5008114 A	April 16, 1991		000	

DESIGNATED-STATES: AT BE CH DE ES FR GB GR IT LI LU NL SE AT BE CH DE ES FR GB GR IT LI LU NL SE

CITED-DOCUMENTS:4.Jnl.Ref; EP 240169 ; US 3923969 ; US 4013785 ; 2.Jnl.Ref

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
EP 336014A	December 2, 1988	1988EP-0120153	
DE 3872382G	December 2, 1988	1988DE-3872382	
DE 3872382G	December 2, 1988	1988EP-0120153	
DE 3872382G		EP 336014	Based on
EP 336014B1	December 2, 1988	1988EP-0120153	
ES 2042700T3	December 2, 1988	1988EP-0120153	
ES 2042700T3		EP 336014	Based on
US 5008114A	November 28, 1988	1988US-0276489	

INT-CL (IPC): A61K 9/18; A61K 9/22

ABSTRACTED-PUB-NO: DE 3872382G
BASIC-ABSTRACT:

Pharmaceutical compsns. comprise a microporous support contg. an active substance in incorporated form. The active substance is distributed within the support pores in crystalline form, the crystal dimensions being in nanometer ranges.

Pref. active substances are diazepam, digoxin, nifedipine, haloperidol etc. The concn. of active substance in soln. is 3-35 g/l and microporous support is added to the soln. in an amt. of 50-250 g/l.

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USE/ADVANTAGE - The pharmaceutical compsns. are useful for prepg. capsules, tablets, transdermal films and pharmaceutical forms for topical use and suppositories. The cqmpsns. are controlled release compsns. The dispersion of the prod. in nanocrystals enables the physical and chemical stability of the medicament to be maintained and results in sharp improvement of the biopharmaceutical properties of the system.

ABSTRACTED-PUB-NO: EP 336014A
EQUIVALENT-ABSTRACTS:

Pharmaceutical compsns. comprise a microporous support contg. an active substance in incorporated form. The active substance is distributed within the support pores in crystalline form, the crystal dimensions being in nanometer ranges.

Pref. active substances are diazepam, digoxin, nifedipine, haloperidol etc. The concn. of active substance in soln. is 3-35 g/l and microporous support is added to the soln. in an amt. of 50-250 g/l.

USE/ADVANTAGE - The pharmaceutical compsns. are useful for prepg. capsules, tablets, transdermal films and pharmaceutical forms for topical use and suppositories. The cqmpsns. are controlled release compsns. The dispersion of the prod. in nanocrystals enables the physical and chemical stability of the medicament to be maintained and results in sharp improvement of the biopharmaceutical properties of the system.

EP 336014B

Pharmaceutical compositions with controlled release comprising a microporous support containing the active substance in incorporated form, wherein the microporous support is chosen from the group of substances comprising silica, silicates, zeolites, alumina, activated carbon and microporous polymer substances having pores of average diameter between 5 and 150nm, a specific surface of between 30 and 600 m2/g and a particle diameter of less than 200 micrometers, characterised in that the active substance is distributed within the support pores in crystalline form with a melting point less than that of the original medicament.

US 5008114A

New controlled release compsns. comprise microporous support with 5-150 mm dia. pores, surface area 40-600 m2/g and particle diam. below 200 microns, of silica, silicates, zeolites, alumina, activated C or microporous polymer with 4-60 % wt. drug distributed within the support pores in crystalline form in nm range (3-100 nm). Drugs include antihypertensives, antiinflammaties, antianxieties, antidepressants, corticosteroids, and antibacterials.

New method of prepn. comprise addn. support to soln. of drug and stirring at RT for 70+ (90-100) hrs., then slow evapn. of solvent at 10-20 deg C below solvent b.pt. at 500760 mm Hg.

Drugs may be of low water-sol and solvents include, water, organics, oils, molten semisolids, CHCl3, acetone, Cl2Et, EtOH, with conc. drug 2-40 g/l. Amt. support is 3-500 g/l soln. Esp. applicable to diazepam, digoxin, grisopulvin, MeOH-progesterone AcO, nifedipine, etc. ADVANTAGE - Structuring drug in crystalline form improves stability. (5pp)n

CHOSEN-DRAWING: Dwg.0/0 Dwg.0/0

DERWENT-CLASS: A96 B05 B07
CPI-CODES: A12-V01; B01-C04; B01-D01; B02-G; B04-C03; B05-A01B; B05-B02C; B05-C06; B06-A03; B06-D07; B06-F03; B07-D04D; B07-D05; B12-M10A; B12-M11H;

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(54) Pharmaceutical compositions with controlled release, and a method for their preparation.

(57) Pharmaceutical compositions comprising a microporous support and an active substance incorporated therein, the incorporation of said active substance being effected by adding the microporous support to a solution of the active substance, stirring the mixture obtained for at least 70 hours at ambient temperature and finally evaporating the solvent slowly.

EP 0 336 014 A1

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PHARMACEUTICAL COMPOSITIONS WITH CONTROLLED RELEASE, AND A METHOD FOR THEIR PREPARATION

Field of the invention

This invention relates to pharmaceutical compositions with controlled release in which the active substance is incorporated in a microporous support.

Prior art

It is known to use microporous supports for incorporating active substances of pharmaceutical type to improve their useful properties.

For example, in order to increase the release rate of poorly soluble medicaments it has been proposed to incorporate them in a porous material either operating with a solution of said medicaments (European Patent Application 0163178) or operating by dry grinding (European Patent Application 0129893).

Again, various authors [DE 3230736, DE 2163034, US 3923969, Rupprecht H et al., Colloid Polym. Sci. (1977) 255-3, pp. 276-84] have suggested the use of porous silicas to obtain prolonged release of the medicament by utilizing the dimensions and shape of the pores or the properties of the medicament adsorption on the silica surface.

In all the stated methods, the medicament is present either in the amorphous state or as microcrystals (dimensional range of the order of micrometres).

Summary of the invention

In the present invention the medicament is structured in crystalline form with crystals having a size of the order of nanometres.

This dispersion of the product in nanocrystals enables the chemical and physical stability of the medicament to be maintained and results in a sharp improvement in the biopharmaceutical properties of the system.

The present invention relates to pharmaceutical compositions and to the method for their preparation.

Said pharmaceutical compositions comprise a microporous support and an active substance incorporated therein and are characterised in that said active substance is distributed in the support pores as nanocrystals; said microporous support having pores of average diameter between 5 and 150 nm, a specific surface of between 30 and 600 m^2/g, a particle diameter of less than 200 microns and the content of said active substance being between 4 and 60% by weight.

Said method is characterised by adding a microporous support to a solution of the active substance, stirring at ambient temperature for at least 70 hours and slowly evaporating the solvent under reduced pressure.

Detailed description of the invention

The pharmaceutical compositions according to the invention are prepared by the following method and have the characteristics stated hereinafter.

A solution of the active substance is prepared, a microporous support is added to this solution and the mixture obtained is kept stirring at ambient temperature for a prolonged time, at least 70 hours and preferably between 90 and 100 hours. After this treatment the solvent is evaporated slowly.

If the stirring time is less than 70 hours the desired active substance release characteristics are not obtained, whereas if the time is extended beyond 100 hours the improvement is negligibl :

Pref rred active substances for the compositions according to the invention are those of low water-solubility, which are released from said compositions at a higher rate than the pure substance. These substances are represented in numerous groups of medicaments such as in anti-hypertensives, anti-inflammatories, anti-anxiety agents, antidepressives, corticosteroids and antibactericides.

Particularly important examples of these substances are diazepan, digoxin, griseofulvin, methylhydroxyprogesterone acetate, nifedipine, megestrol acetate, haloperidol, nicardipine, diltiazem and etoposide.

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The solvents usable for the active substances are water, organic solvents, oils and molten semisolids, of which those preferred are chloroform, acetone, dichloroethane and ethyl alcohol. The solvent choice is made on the basis of the characteristics required for the composition.

Any substance compatible with the medicament can be used as the microporous support, for example silicas, silicates, zeolites, aluminas, activated carbons and microporous polymer substances.

The microporous supports must have an average pore diameter of between 5 and 150 nm and preferably between 7 and 110 nm, with a specific surface of between 30 and 600 m^2/g and a particle diameter of less than 200 µm.

The active substance concentration in the solution depends on the solvent used and is preferably close to the saturation concentration. For example using chloroform, the concentration is between 2 and 40 g/l and preferably between 30 and 35 g/l, and the quantity of microporous support added is between 3 and 500 grams per litre of solution and preferably between 50 and 250 grams per litre of solution. After stirring the suspension, the solvent is removed by slow evaporation at a temperature of 10-20° C less than the solution boiling point and at a pressure of between 500 and 760 mmHg (66.500 - 101.000 Pa).

The solid material obtained is disintegrated until a powder is obtained with a particle size of less than 200 microns and is heated in an oven at 20-30° C under vacuum to remove the solvent traces.

In the composition obtained in this manner the active substance has nanocrystal dimensions with a diameter of between 3 and 100 nm, and a melting point less than that of the same solid of coarser dimensions.

The pharmaceutical compositions according to the invention have the following advantages over compositions obtained by known methods:

a) improved biopharmaceutical properties of the medicament due to its increases solubility which is related to the reduction in crystal dimensions by the known Kelvin equation:

$$\frac{S^*}{S^\circ} = \exp\left(\frac{2\gamma v}{RTr^*}\right)$$

where S^* is the solubility of finely divided crystals of radius r^*, S° is the solubility of crystals of the same solid but of coarse dimensions, γ is the solid/liquid interfacial tension, v is the molar volume of the solid, R is the universal gas constant and T is the absolute temperature;

b) in parallel with the lowering of the melting point of the medicament there are also considerable modifications in the rate of release of the medicament, which is more prolonged and controlled (release mechanism of zero order);

c) compared with systems containing the medicament in amorphous form, the compositions according to the invention containing the crystalline medicament with a lowered melting point not only have improved dissolving characteristics but also have increased chemical and physical stability. In this respect it is well known that amorphous products tend to crystallize with time, with resultant deterioration in their passage into solution.

The compositions according to the present invention can be used for preparing capsules, pharmaceutical forms for topical use, suppositories, tablets and transdermal films, and can contain the conventional excipients such as binding agents, fillers, lubricants, disintegrating agents, wetting agents, flavourings and colorants. For example they can contain substances such as gelatin, sorbitol, lactose, starch, magnesium stearate and sodium lauryl sulphate.

The following examples of the preparation and characteristics of the compositions according to the invention are given by way of non-limiting illustration.

EXAMPLE 1

A solution of griseofulvin in chloroform and a solution of methylhydroxyprogesterone acetate (MHPA) in chloroform were prepared with a concentration of 35 g/l and 150 g/l respectively. 50 g of microporous silica gel with average pore radius 3.3 nm, specific surface 497.6 m^2/g and particle size between 8 and 200 microns were added to 1 litre of griseofulvin solution and to 200 ml of MHPA solution.

In each case, the suspension obtained was kept stirring at ambient temperature for 96 hours. The

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solvent was then removed by evaporation at a temperature of 45° C and a pressure of 700 mmHg (93.100 Pa) in a rotary evaporator until a product of powder form was obtained. This product was disintegrated to a particle size of between 8 and 200 microns and heated in an oven to 30° C under vacuum for 12 hours to eliminate all solvent traces.

The product obtained was subjected to the active substance release test using the USP XX paddle method under sink conditions, with 900 ml of buffer solution of pH 7.5 for the griseofulvin and of pH 5.5 for the MHPA, at 37° C and at 150 r.p.m.

The product was also subjected to differential thermal analysis (D.S.C.) to determine its melting point and crystal size.

The thermal and dimensional characteristics of the two preparations are given in the following table:

	melting point (° C)	- ΔT on original medicament (° C)	Crystal diameter (nm)
Preparation with griseofulvin	123	96.8	4.0
Preparation with MHPA	113.5	92.6	5.2

The results of the dissolving test are given in the following table:

Time (minutes)	a) griseofulvin in solution (μg/ml)	b) MHPA in solution (μg/ml)
30	1.45	0.12
60	2.10	0.17
90	2.75	0.22
120	3.25	0.26

EXAMPLE 2 (comparison)

Example 1 was repeated but with the difference that the suspension of microporous silica in the solution of active substance was kept stirring for 24 hours.

The thermal and dimensional characteristics of the two products are given in the following table:

	melting point (° C)	- ΔT on original medicament (° C)	Crystal diameter (nm)
Preparation with griseofulvin	206.2	13.6	30.0
Preparation with MHPA	198.5	7.6	40.0

The results of the active substance release test are given in the following table:

Time (minutes)	a) griseofulvin in solution (μg/ml)	b) MHPA in solution (μg/ml)
30	1.60	0.13
60	2.50	0.20
90	3.61	0.29
120	4.55	0.37

EXAMPLE 3

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Example 1 was repeated but with the difference that a microporous silica was used having an average pore radius of 7.7 nm.

The thermal and dimensional characteristics of the medicament crystals contained in the two products are given in the following table:

	melting point (°C)	- ΔT on original medicament (°C)	Crystal diameter (nm)
Preparation with griseofulvin	184.8	35.0	10.8
Preparation with MHPA	169.9	36.2	15.1

The results of the active substance release test are given in the following table:

Time (minutes)	a) griseofulvin in solution (µg/ml)	b) MHPA in solution (µg/ml)
30	1.45	0.12
60	2.10	0.17
90	2.75	0.22
120	3.25	0.26

EXAMPLE 4 (comparison)

Example 3 was repeated but with the difference that the suspension of microporous silica in the solution of active substance was kept stirring for 24 hours.

The thermal and dimensional characteristics of the medicament crystals contained in the two products are given in the following table:

	melting point (°C)	- ΔT on original medicament (°C)	Crystal diameter (nm)
Preparation with griseofulvin	206.2	13.6	30.0
Preparation with MHPA	198.5	7.6	40.0

The results of the active substance release test are given in the following table:

Time (minutes)	a) griseofulvin in solution (µg/ml)	b) MHPA in solution (µg/ml)
30	2.75	0.22
60	4.30	0.35
90	5.25	0.42
120	5.70	0.46

EXAMPLE 5

35 g of microporous silica gel with an average pore radius of 7.7 nm were added to 1 litre of a solution of griseofulvin in acetone at a concentration of 25 g/l. The suspension obtained was kept stirring at ambient tempeature for 96 hours and the solvent was then removed by evaporation at 35° C and a pressure of 600 mmHg (79.800 Pa) in a rotary evaporator until a product of powder form was obtained.

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This product was disintegrated to a particle size of between 8 and 200 microns and left under vacuum at ambient temperature for 12 hours to eliminate solvent traces.

The product obtained is in the form of crystals with a melting point of 203.5° C and a size of 25 nm. The results of the active substance release test are given in the following table:

Time (minutes)	griseofulvin in solution (µg/ml)
30	2.00
60	3.30
90	4.35
120	5.28

EXAMPLE 6

70 g of microporous silica gel with an average pore radius of 7.7 nm were added to 1 litre of a solution of griseofulvin in 1,2-dichloroethane at a concentration of 50 g/l. The suspension obtained was kept stirring at ambient temperature for 96 hours and the solvent was then removed by evaporation at 60° C and a pressure of 500 mmHg (66.500 Pa) in a rotary evaporator until a product of powder form was obtained.

This product was disintegrated to a particle size of between 8 and 200 microns and left under vacuum at ambient temperature for 12 hours to eliminate solvent traces.

The product obtained is in the form of crystals with a melting point of 219.8° C (same melting point as original medicament) and a size of the order of microns.

The results of the active substance release test are given in the following table:

Time (minutes)	griseofulvin in solution (µg/ml)
30	1.60
60	2.15
90	2.50
120	2.70

Claims

1. Pharmaceutical compositions comprising a microporous support containing the active substance in incorporated form, characterised in that said active substance is distributed within the support pores in crystalline form, the crystal dimensions being in the nanometre range.

2. Compositions as claimed in claim 1, characterised in that said active substance crystal dimensions are between 3 and 100 nm.

3. Compositions as claimed in claim 1, characterised in that the content of said active substance is between 4 and 60% by weight.

4. Compositions as claimed in claim 1, characterised in that said microporous support has pores of average diameter between 5 and 150 nm, a specific surface of between 30 and 600 m^2/g and a particle diameter of less than 200 microns.

5. Compositions as claimed in claim 1, characterised in that said microporous support is chosen from the group of substances comprising silica, silicates, zeolites, alumina, activated carbon and microporous polymer substances.

6. Compositions as claimed in claim 1, characterised in that said active substance is a substance of low water solubility.

7. Compositions as claimed in claim 1, wherein said active substance is diazepan, digoxin, griseofulvin, methylhydroxy-progesterone acetate, nifedipine, megestrol acetate, haloperidol, nicardipine, diltiazem or etoposide.

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8. Compositions as claimed in claim 1, containing conventional excipients such as gelatin, sorbitol, lactose, starch, magnesium stearate and sodium lauryl sulphate.

9. A method for preparing pharmaceutical compositions, characterised by adding a microporous support to a solution of the active substance, stirring at ambient temperature for at least 70 hours, then slowly evaporating the solvent at a temperature of 10-20° C less than the solution boiling point and a pressure of between 500 and 760 mmHg (66.500 - 101.000 pa).

10. A method as claimed in claim 9, characterised in that said microporous support is chosen from the group comprising silica, silicates, zeolites, alumina, activated carbon and microporous polymer substances.

11. A method as claimed in claim 9, characterised in that said microporous support has pores of average diameter between 5 and 150 nm and preferably between 7 and 110 nm, a specific surface of between 30 and 600 m^2/g and a particle size of less than 200 microns.

12. A method as claimed in claim 9, characterised in that said active substance is a substance of low water solubility.

13. A method as claimed in claim 9, characterised in that the solvent for said solution of the active substance is chosen from the group comprising water, organic solvents, oils and molten semisolids, and preferably from chloroform, acetone, dichloroethane and ethyl alcohol.

14. A method as claimed in claim 9, characterised in that the active substance concentration in said solution is between 2 and 40 g/l and preferably between 30 and 35 g/l.

15. A method as claimed in claim 9, characterised in that the quantity of said microporous support added to said solution is between 3 and 500 grams per litre of solution and preferably between 50 and 250 grams per litre of solution.

16. A method as claimed in claim 9, characterised in that said stirring at ambient temperature is conducted preferably for 90-100 hours.

17. The use of pharmaceutical compositions claimed in claim 1 for preparing capsules, tablets, transdermal films, pharmaceutical forms for topical use and suppositories.

Claims for the following Contracting States: GR, ES

1 A method for preparing pharmaceutical compositions, characterised by adding a microporous support to a solution of the active substance, stirring at ambient temperature for at least 70 hours, then slowly evaporating the solvent at a temperature of 10-20° C less than the solution boiling point and a pressure of between 500 and 760 mmHg (66.500 - 101.000 pa).

2 A method as claimed in claim 1, characterised in that said microporous support is chosen from the group comprising silica, silicates, zeolites, alumina, activated carbon and microporous polymer substances.

3 A method as claimed in claim 1, characterised in that said microporous support has pores of average diameter between 5 and 150 nm and preferably between 7 and 110 nm, a specific surface of between 30 and 600 m^2/g and a particle side of less than 200 microns.

4 A method as claimed in claim 1, characterised in that said active substance is a substance of low water solubility.

5 A method as claimed in claim 1, characterised in that the solvent for said solution of the active substance is chosen from the group comprising water, organic solvents, oils and molten semisolids, and preferably from chloroform, acetone, dichloroethane and ethyl alcohol.

6 A method as claimed in claim 1, characterised in that the active substance concentration in said solution is between 2 and 40 g/l and preferably between 30 and 35 g/l.

7 A method as claimed in claim 1, characterised in that the quantity of said microporous support added to said solution is between 3 and 500 grams per litre of solution and preferably between 50 and 250 grams per litre of solution.

8 A method as claimed in claim 1, characterised in that said stirring at ambient temperature is conducted preferably for 90-100 hours.

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European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 88 12 0153

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
X	EP-A-0 240 169 (SDS BIOTECH UK, LTD) * Page 3, lines 49-51; page 7, lines 38-41 *	9,13,16	A 61 K 9/18 A 61 K 9/22
X	US-A-4 013 785 (WEINTRAUB et al.) * Claim 2 *	9,17	
D,X	US-A-3 923 969 (BAUKAL et al.) * Abstract *	1	
X	CHEMICAL ABSTRACTS, vol. 94, no. 4, January 1981, page 306, abstract no. 20347n, Columbus, Ohio, US; K. UNGER et al.: "Incorporation of drugs in polycondensates of polyethoxysiloxane for mediating release of the active substance. I. Basis of the process and characterization of the pharmaceutical carrier (part 1)", & PHARM. IND. 1980, 42(10), 1027-30 * Abstract *	1	
Y	IDEM	4	TECHNICAL FIELDS SEARCHED (Int. Cl.4) A 61 K
Y	CHEMICAL ABSTRACTS, vol. 81, no. 12, 23th September 1974, page 335, abstract no. 68486r, Columbus, Ohio, US; H. RUPPRECHT et al.: "Effect of pore structure of silica on the availability of drugs", & PHARM. IND. 1974, 36(4), 260-3 * Abstract *	4	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	17-03-1989	DULLAART A.W.M.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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